UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,138	01/08/2007	Jerome B. Zeldis	9516-352-999	5513

20583 7590 09/29/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,138	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicant submitted a preliminary amendment on 8/13/2008 that did not get entered into the application prior to the previous Office Action being mailed. Accordingly, the Non-Final Office Action mailed 8/26/2008 is hereby **vacated** and replaced in its entirety with the present Office Action.

Applicant's preliminary amendment filed 8/13/2008 is acknowledged and entered. Claims 1-9 are cancelled and claims 10-24 are newly added. Claims 10-24 are presented for examination and are the subject of this Office Action.

Priority

This application is a 371 of PCT/US/2004/037083, filed November 4, 2003, and claims priority to U.S. Provisional Application No. 60/517,405, filed November 6, 2003.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 10/24/2006. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Newly added claims 12 and 13 recite a method of treating idiopathic pulmonary fibrosis comprising administering thalidomide in combination with an anti-inflammatory agent, a COX-2 inhibitor, or a steroid (claim 12), specifically reciting the active agents prednisone, cyclophosphamide, or interferon (claim 13). There is no support in the specification for such a method, wherein thalidomide is administered in combination with these recited agents for the treatment of idiopathic pulmonary fibrosis.

While Applicants disclose that second active agents can be administered with thalidomide for the treatment of angiogenesis related disorders (page 7, lines 19), the disclosure of such disorders in the immediately preceding paragraph (page 6, lines 25-34) does not list idiopathic pulmonary fibrosis. Further, the disclosure of second active agents recited at page 10, line 1 to page 16, line 10 lists anti-inflammatory agents, COX-2 inhibitor (page 12, line 17), and a steroid (page 12, lines 9 and page 16, line 3), as well as the specifically recited prednisone (page 15, line 5), cyclophosphamide (page 16, line 3), or interferon (page 11, lines 1-2) are listed as anti-cancer drugs, not drugs to treat idiopathic pulmonary fibrosis. Further still, while Applicants disclose celecoxib as a "COX-2 inhibitor", there is no disclosure of combining thalidomide with COX-2 inhibitors generally as recited in the claims.

Accordingly, the claims introduce new matter because no where in Applicant's disclosure is a combination of thalidomide and an anti-inflammatory agent, a COX-2 inhibitor, or a steroid (claim 12), specifically the active agents prednisone, cyclophosphamide, or interferon (claim 13), for the treatment of idiopathic pulmonary fibrosis disclosed. In fact, in the specific embodiments disclosed at pages 20-24, which disclose combinations of thalidomide with second active agents for the treatment of specific diseases, there is not a single embodiment for the treatment of idiopathic pulmonary fibrosis with thalidomide and a second active agent.

Claims 10-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of thalidomide or a pharmaceutically acceptable salt or sterioisomer thereof, does not reasonably provide enablement for a "*solvate*" of thalidomide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The claims recite administration of a "solvate" of thalidomide. The term "solvate" cover various forms of thalidomide at different proportions of water or solvents. Thus, the scopes of the above claims are unduly broad because solvates encompass thalidomide solvated with any solvent in any ratio of thalidomide to solvent.

The specification does not define what a "solvate" is and it does not provide working examples to guide the skilled chemist to make a solvate of thalidomide. There is no guidance on what proportion of water or solvent to use for obtaining a "solvate". Thus, the specification fails to provide sufficient enablement for making the claimed solvates of thalidomide.

Although it is not unusual to expect a "solvate" of a compound to form, the process for selecting a particular solvate is not standard for all drugs. Furthermore, the teaching of Vippagunta (Adv. Drug Del. Rev., Vol. 48, (2001), pp. 3-26) flatly states on page 18, section 3.4 the following:

> "Predicting the formation of solvates or hydrates of a compound...is complex and difficult."

Thus, the state of the prior art does not support the broad scope of the above claims.

Even with the advanced training, the skilled clinician would have to engage in extensive research to select a particular "solvate" of thalidomide and determine which solvates, if any, have the therapeutic activity recited in the instant claims.

The process of making a "solvate" is quite unpredictable because it is not possible to predict whether solid solutions will form and at what stoichiometry proportion (*i.e*, one, two, or half a molecule of solvent added per molecule of host). Thus, with such a limited teaching from the specification and the art, the skilled chemist would have to engage in undue experimentation to make and use the claimed "solvate" of thalidomide as recited in the instant claims.

Claims 10-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of idiopathic pulmonary fibrosis comprising administering thalidomide alone or in combination with other active agents (e.g., prednisone, cyclophosphamide, or interferon).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art,

the examiner cites Nagai *et al.* (Expert Opin. Pharmacother., 2008, vol. 9, no. 11, pages 1909-1925) and Meltzer *et al.* (Orphanet Journal of Rare Disease, 2008, vol. 3, no. 8)[2].

Nagai *et al.*, cited for evidentiary purposes, teaches that all currently available therapeutic trials on interstitial pulmonary fibrosis (IPF) are severely limited by gaps in the understanding of the natural history of the disease (page 1910, left column) and there is no good evidence to support the routine use of any specific therapy in the management of IPF (id., right column). Further, even among responders to corticosteroid therapy, the disease relapses and progresses after the initial response (id.). Cyclophosphamide, recited in claim 13 as a second active agent for the treatment of IPF, has been administered to IPF patients (page 1912, left column) and was of limited efficacy. With regard to interferon, also recited as a second active agent in claim 13, retrospective studies on IFN-γ for the treatment of IPF have been completed and show very limited benefit (page 1913, right column). Table 3 of Nagai et al. shows the results of completed clinical trials of numerous agents for the treatment of IPF. Four out of the six trials resulted in a negative primary outcome. The authors conclude that if asked to identify which immunosuppressive drugs are better for IPF patients, no confident answer can be given (page 1920, right column).

Meltzer et al., also cited for evidentiary purposes, teach that IPF is difficult to diagnose (pages 2-3 and 8-9) and that the term "idiopathic" suggests that there are no known causes for IPF (page 4, right column). With regard to medical treatment of IPF, Meltzer et al. teach that current medical therapy is poorly effective, at best (page 10, left column). With regard to the unpredictability of treating IPF with pharmacological drugs, Meltzer et al. teach that experience has shown that although a drug may appear promising in small Phase II trials, large trials with additional power to determine efficacy may, in fact, reveal a drug is ineffective (page 12, left column). In conclusion, the authors state that IPF remains a disease for which the etiology is unknown and the pathogenesis only poorly understood (page 13, left column). Further, the authors teach that there is no definitive approach to the treatment of IPF because evidence for effective medical therapy is still lacking (id.).

---

[2] Meltzer et al. is a pre-publication and thus does not have page numbers. The page numbers referred to by the Examiner are pages 1-15 of the web publication accessed from http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18366757 on Sept. 24, 2008.

These articles plainly demonstrate that the art of treating idiopathic pulmonary fibrosis, particularly in humans, is extremely unpredictable, particularly in the case of a single compound being used to treat this poorly understood disease.

2. The breadth of the claims

The claims are relatively narrow, being drawn to the treatment of idiopathic pulmonary fibrosis comprising administering thalidomide alone, or in combination with other active agents.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no specific direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat idiopathic pulmonary fibrosis, particularly in humans. In fact, the specification is primarily directed to the treatment of cancer and the only mention of idiopathic pulmonary fibrosis is found in a list of diseases "associated with undesired angiogenesis" (page 17, line 26 to page 18, line 12, especially page 18, lines 6-7). The single working example is limited to demonstrating that *in vitro*, thalidomide enhances the degradation of TNF-α mRNA. Although broad doses and administration routes of thalidomide are described in the specification, these doses and administration routes are contemplated to be useful for the treatment of all angiogenic-related conditions. No reasonably specific guidance is provided concerning useful therapeutic protocols for any specific conditions or diseases, particularly the treatment of idiopathic pulmonary fibrosis as recited in the instant claims.

Further, there are no *in vitro* or *in vivo* experimental models of any diseases described, including idiopathic pulmonary fibrosis. While the administration routes disclosed in the specification are standard routes of administration for therapeutic agents, Applicant has provided no specific administration regimens (*e.g.* timing, specific doses, etc.) necessary to treat any specific disease.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that thalidomide could be predictably used to treat idiopathic pulmonary fibrosis as recited in the instant claims.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicant has presented a general idea that because thalidomide inhibits angiogenesis it must therefore, *a priori*, be useful in the treatment of idiopathic pulmonary fibrosis. However, there is no evidence of record that idiopathic pulmonary fibrosis is caused by angiogenesis. In fact, the evidentiary documents cited supra teach that idiopathic pulmonary fibrosis is poorly understood and the etiology not clear. As such, there is nothing in the prior art or Applicant's disclosure that would lead one to believe that thalidomide would have any efficacy in the treatment of this disease.

Given the extremely diverse diseases contemplated to be treatable by thalidomide and the limited examples provided in the specification, the skilled artisan cannot predict what specific disease may or may not be amiable to treatment with thalidomide, including idiopathic pulmonary fibrosis. At best, Applicant has provided the skilled artisan with the guidance to randomly test thalidomide for the treatment of a plethora of diseases, with no assurance or reasonable expectation of success.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614